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Division of Dockets Management (HFA - 305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Docket Number 2005D-0030

Re: Draft Guidance for Industry on Clinical Lactation Studies—Study Design, Data Analysis, and Recommendations for Labeling

From Eli Lilly and Company

Eli Lilly and Company (Lilly) appreciates the opportunity to offer the following comments to the Food and Drug Administration regarding the Draft Guidance for Industry on Clinical Lactation Studies—Study Design, Data Analysis, and Recommendations for Labeling. In particular, Lilly is pleased to see a proposed guidance on:

1. Clinical lactation studies.
2. Possible study designs for use in clinical studies.
3. Recommendations of when to do a study.

General comments and concerns regarding broad-based recommendation of clinical lactation studies:

This Draft Guidance provides considerable analysis regarding the design and analysis of clinical lactation studies and associated labeling recommendations, but engages in relatively little analysis of the issue of *whether* clinical lactation studies should be conducted for a particular compound. Despite this limited analysis, the Draft Guidance proceeds to "recommend" that such studies be conducted in four potentially quite broad situations (lines 139-148). Procedurally, Lilly is concerned that any FDA position on the necessity of such studies for populations to whom the manufacturer does not seek authorization to market is inappropriate for introduction in this Draft Guidance. Substantively, Lilly believes that much greater consideration needs to be given to the relative merits and risks of, and alternatives to, such studies than is presented in this Draft Guidance. Accordingly, Lilly recommends that the Guidance be modified to remove the blanket recommendation of conducting clinical lactation studies in the four situations set out in lines 139-148 and to either focus exclusively on study design, data analysis and labeling issues or to restrict the discussion of whether to conduct studies to an introduction of the issues and factors one might consider in a given situation.

Lilly believes that there must be a greater emphasis on assessing for a specific drug the need for such data and all the alternative sources of information other than conducting clinical lactation studies, particularly studies that would involve nursing infants and offer no potential therapeutic benefit to mother or child. Specifically, any discussion in the Guidance should align with the following initial considerations:

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1. Assess the rationale and known properties of the drug anticipated to be used by nursing mothers,
   a. The analysis of need should begin with review of non-clinical studies to ascertain any signals that require special consideration.
   b. The assessment should include a theoretical discussion of the pharmacokinetics and pharmacodynamics of the drug, the nature and extent of the anticipated use of the product by nursing mothers, and the potential for meaningful drug exposure for the nursing infant.
   c. Part of this assessment needs to include consideration of a meaningful impact on the clinical drug use in nursing mothers. If the change in PK or PD would need to be extremely large, then performing specific studies in a nursing population may not be justifiable or may point to limiting the study to a much simpler "confirm" design.
2. Consider the power of modeling to determine possible dose and timing adjustments to achieve clinically meaningful outcomes while minimizing potential infant exposure.
3. Only after the above assessment, if there are no satisfactory alternatives, should the discussion turn to the possibility of adequately designed studies that will result in clinically meaningful outcomes.

A part of each of the above discussions needs to include a thorough benefit-to-risk analysis.

The guidance document provides a limited discussion regarding the issues of ethics and of risk. Prior to reaching a conclusion as to the appropriateness of undertaking PK research in nursing mothers and infants, there should be a clear assessment as to what are the potential risk to the mother and the child, what is known about the drug's disposition and effects in non-nursing adults and in children, what are the theoretical or possible effects of nursing on these parameters, and what are the key PK, PD and safety issues to be addressed in the research plan. This background information is needed to provide the framework for developing an appropriate research plan, the implementation of which provides informative results regarding dosing in as safe and ethical manner as is possible.

Finally, while Lilly recognizes the value of data derived from controlled clinical studies, conducting such PK studies in nursing mothers and their infants present considerable practical challenges. The actual or perceived risk uncertainties associated with infant exposure to pharmaceutical products may well lead sponsors, Institutional Review Boards, clinical investigators, and patients reluctant or unwilling to participate in such research, particularly in any studies in which there is not a clear and important potential therapeutic benefit to the participating women and/or their infants.

Additional general concerns and suggestions:

1. This guidance is consistent with research in the area of drugs in breast milk. There is a general tone in the guidance that lactating women will have substantial changes or difference in the Pharmacokinetics (PK) of drugs. This certainly is a reasonable possibility based upon the variety of known physiological changes

associated with the post-partum period. The question then becomes, do such changes or differences occur for most drugs or is this more of a theoretical possibility that is not frequently the outcome. Another question concerns the degree of changes in the Pharmacokinetics of lactating or post-partum women and the need for dosing modifications in this special population. The perspective of the guidance therefore overplays the potential importance of these changes. If it is true that in the majority of the cases there are not substantial PK or PD differences, then the role of a guidance fits more with providing help on those "typical" cases and not giving an inordinate focus on more rare circumstances. For example, it would be helpful to set the typical expectation and discuss the research designs for the typical drug and then discuss the need to more elaborate consideration to be given for rare or special circumstances.

2. The sample size section focuses on sizing the study based on maternal PK variability. However, this is typically not the focus of these studies. While one would definitely be interested in the maternal PK while doing the study, it appears as though the focus should be on measuring the amount of drug secreted in the milk and the theoretical dose the infant would receive. These studies are extremely difficult to recruit and should be sized similar to a pilot study (6-12 subjects).
3. There are actually several methods described to estimate the potential dose that an infant might ingest in breast milk. The concern here is that the guidance is silent about how to reconcile or at least address possible differences in the estimated infant dose. The guidance permits some flexibility in calculation but then limits this flexibility by saying that the estimates should be comparable to those in the guidance. More flexibility to alternatives should be acceptable provided that alternative calculations can be justified.
4. The section on future research goes back to the topic about preclinical data and modeling. This seems to contradict an earlier statement that preclinical and modeling data are not predictive of human conditions and therefore does not obviate the need for human data.
5. Formulas are provided in the document for calculation of infant exposure based on data from the Plasma and Milk study. This should provide useful information for decision-making with regard to breast-feeding, without exposing infants to potentially harmful substances during the critical postnatal development stage. Granted, this does not provide PD information for infants, but modeling can be conducted for fetal compartments. The guidance clearly outlines the important advantages of breast-feeding; however, bottle-feeding is a viable alternative during the period that the mother would be enrolled in a lactation clinical trial. Calculation of potential infant exposure based on maternal data and modeling based on knowledge of fetal physiology and previous experience with environmental chemicals should provide an adequate basis for evaluation of infant safety.

Possible Gaps in the Guidance Document:

1. What is the reasonable "cut off" where the amount of drug in breast milk is more than could be anticipated? From a general survey of the literature, it appears as though this value is around the region of 1% of the maternal dose. When more than this is found in breast milk, then more studies may be advisable before any recommendation is made for breast-feeding infants while taking such a drug. When no more than this amount is found, then one can presume that what appears is a fractional component of the maternal body load.
2. Have bioanalytical issues been addressed adequately? There are some possible problematic areas in the assay of breast milk as a biological medium such as homogeneity of the sample and partitioning of the drug into more aqueous or the more lipid portions of milk.
3. Is there guidance for differences in the interpretation and value of preclinical (animal) and clinical (human) study data and how these should be incorporated into labeling? Are data available on the secretion of radio labeled drugs into breast milk (animal data) of value?
4. Are there some categories of drugs, which would likely never be administered if the mother is nursing a baby, for example oncolytics?
5. Ethical Issues: It seems very difficult ethically to justify including the infant sampling portion of these studies, unless the drug has already been investigated and used in this population and is known to be safe. This is assuming the sponsor is not recommending use in lactating women, which is usually the case. This vulnerable population should be handled separately and if the PD and bioavailability needs to be determined this should be done in a separate infant-only study at doses that are likely to provide adequate data.
6. The section on developing dosage recommendations gives two alternatives for judging whether or not a dose adjustment would be necessary. These are both fairly conservative and restrictive approaches. Once again, some additional leeway perhaps should be considered but with the most critical requirement being that any approach should be pre-specified and not just a post-hoc assessment.
7. A key item missing from the document is what types of non-clinical safety data would support the proposed clinical trial designs. Although the document appears to dismiss the value of non-clinical models that might be applicable to clinical lactation studies, it is still necessary to establish safety in the trial population.
8. Lines 714-722 indicate that non-clinical models of lactation exposure could be validated by clinical data. If non-clinical models are shown to be predictive, could they replace clinical studies? What role would they serve in future drug development?
9. Lines 609-610 states that "non-positive" findings indicate failure to detect an impact of lactation on PK or PD. Exactly what does this mean? Is the assumption that there is no safe dose, and if so, how is this different from what is currently stated in most labels?

Section specific comments for the FDA:

1. Line 151 states, "if drugs are not used in lactating women of reproductive age, then clinical studies in lactation are usually not needed. The suggestion is to delete the word "usually" as these studies are never needed.
2. Line 167-169 of the guidance document describes situations where it may be "advisable to conduct lactation studies" even for a drug with infrequent use or in rare conditions. Given the ethical and operational constraints on conducting these studies, a better approach may be to develop strategies that will minimize the potential drug exposure to the infant, such as recommending pumping of milk for a period of time adequate to pass through a time period when an infrequent drug is used (ie. radioimaging agent, vaccine, or other acute use/infrequent use drug) rather than to suggest that lactation studies need to be conducted in such circumstances. It seems reasonable to formulate recommendations based upon the PK properties of the drug's systemic exposure profile by establishing how long a period is necessary until the body system has essentially eliminated the drug or until the risk of exposure to the infant is minimized.
3. Line 171-174 suggests that animal-models and other predictive models "do not help" in deciding whether to conduct a lactation study. This is counter to the FDA's approach for the critical path initiative and other drug research enabling activities in which the agency is involved. Animal studies and non-clinical models may be very helpful and can potentially be predictive of certain situations that require more or less evaluation. Furthermore, such models can be used to help design studies rather than simply guessing how to do design the lactation study. These statements in the guidance need to be re-evaluated and revised.
4. Line 217-218 mentions frequent collection of samples from the mother and infant. Are there guidelines to indicate what would be excessive? If so, they should be referenced in the document.
5. Line 219 discusses mother-infant pairs and the fraction of the drug that is systemically available to the breast-fed infant. This is very difficult to estimate in normal healthy subjects given just a simple oral dose (without IV data) so this expectation that this information could be obtained from concentration measurements in the infant would seem to be virtually impossible. At best, concentration measurements in the infant only provide the magnitude of drug exposure (AUC or Cmax) that possibly can be calibrated to other safety or exposure data.
6. Line 220 states that "the total clearance of the drug or metabolite by the breast-fed child can be estimated as well." This would be a technical challenge since the infant dose is not known exactly (only can be asserted from the amount of drug in breast milk and the amount of milk consumed by the infant). The "estimation of clearance" would be very compromised and perhaps not represent a valid determination.
7. Line 274-276 also discusses short half-life and sporadic or intermittent use drugs (ie for migraine). This again seems to be a situation where lactation studies may not be needed since reasonable strategies can be described that will minimize drug exposure to the nursing infant.
8. Line 291 describes a longitudinal study design, which suggests determining PK/PD and milk transfer over time (2-3 months vs. 5-6 months postpartum vs.

after weaning). This seems exceedingly difficult for recruitment and study conduct, and more importantly is not likely to provide meaningful information for dosing purposes. Large differences between these time intervals would not be expected.

9. Line 346 discusses using a control group of lactating female volunteers to evaluate the drug effect on milk production and composition. This seems like a very unreasonable comparison given the between subject variability on milk production and composition. If this information is needed, it may be more beneficial to use only a within-subject comparison.
10. Line 402 recommends that the total and unbound concentration be determined. Is the intent to collect a plasma sample and perform an ex vivo plasma protein binding assay to determine binding in that individual? This information is not used for the critical calculations of infant dose, and would likely not be useful for interpretation of dose adjustments needed in lactating women. Therefore this suggestion should be removed from the guidance, since it is a piece of information that will not address the objectives of the study.
11. Line 391-400 suggests using a procedure to weigh a baby before and after breast-feeding to determine the amount of breast milk that is consumed as a method to estimate the dose of drug in breast milk. Such a procedure is impractical and likely to be very inaccurate. It seems that the pre to post feeding will be only in the several hundredth of grams at most and it would be very unlikely that the weight change would even be detected let alone accurately measured in such circumstances.
12. Line 402-414 discusses "total and unbound concentrations" and "noninvasive sampling" from the perspective of being feasible. Both of these are discussed in drug development programs and maybe appropriate and feasible for a handful of drugs out of thousands. But often the feasibility and practicality of these aspects are beyond what is necessary (or feasible) to appropriately understand and characterize a drug's PK properties. Measuring both total and unbound drug as well as using specialized noninvasive samples is rare in drug development. Therefore, again from the perspective of being generally applicable to most cases, these guidance discussions are not realistic expectations. These special techniques and processes are difficult enough to accomplish in adult subjects or animals given full doses or even super therapeutic doses, let alone in an infant where the dose is typically only a very small fraction of the maternal dose.
13. In addition, line 406 of this guidance suggests that it is important to assay milk samples for milk fat, however, this does not appear to address the objectives of this type of study.
14. Line 418-424 discusses "population PK". This approach and technique in drug development is commonly used. However, this does not seem like the right tool for studies in a small number of study participants. Lactation studies would rarely involve hundreds of patient nor are the data collected in such studies particularly well suited for a population PK analysis. While the population study approach (sparse sampling in a larger number of participants) is a useful design and process for drug development it is not likely to be typically used in lactation studies except in rare or specific circumstances.

15. Lines 462-464 indicate that the Agency recommends total and unbound plasma and milk concentrations be used to estimate PK parameters of parent drug and metabolites. This requires clarification with regard to the importance of metabolites, and whether the recommendation is to assay them separately. This would be a tremendous analytical effort to not only validate assays for metabolites in plasma, but also in milk. We recommend that the agency clarify their guidance in regard to measurement of metabolites and provide a position consistent with the concepts presented in previous ICY and other published guidance documents on the measurements of metabolites (Baillie, T, et al. 2002) (ICH Harmonised Tripartite Guideline. 1994).[1,2]

Sincerely,

Eli Lilly and Company

Paula Long

Paula Long, RN
Global Product Safety
Pregnancy Task Force
Pharmacoepidemiology and Analytical Methods

References:

[1]International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). 1994. ICH harmonized tripartite guideline. Note for guidance on toxicokinteics: the assessment of systemic exposure in toxicity studies.

[2]Baillie T, Cayen M, et al. Contemporary issues in toxicology: drug metabolites in safety testing. Toxicology and Applied Pharmacology. 2002. 182(3): 188-196.